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Association between fibromyalgia syndrome and MTHFR C677T genotype in Turkish patients

Türk hastalarda fibromiyalji sendromu ile MTHFR C677T genotip arasındaki ilişki

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Abstract

Aim: Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and tender points. Among the several suggested mechanisms, most reports strongly emphasize the importance of the molecular mechanisms. It is known that the disorder is accompanied by various mental disorders, the most common being depression. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism was also associated with psychiatric disorders such as depression, anxiety, bipolar disorder and schizophrenia. This study aimed to evaluate the association between C677T genotype of methylenetetrahydrofolate reductase (MTHFR) gene, FMS risk and symptom severity in Turkish patients.

Methods: One hundred (n=100) patients with FMS diagnosed according to the 1990 American College of Rheumatology Classification Criteria were included in our case-control study. Control group consisted of 100 patients of similar age and gender. Genomic DNA was extracted from peripheral blood leukocytes obtained from the participants and MTHFR C677T mutation was detected with real-time polymerase chain reaction. FMS disease activity was evaluated by Fibromyalgia Impact Questionnaire (FIQ) and presence of depression was assessed by Beck Depression Inventory (BDI).

Results: The study and control groups were all female. Depression was detected in 42% of the study group. Results of statistical evaluation have shown that those who carry the 677 C allele are 2.111 times more likely to have FMS than those with the T allele of MTHFR (P<0.001). There was no relationship between distribution in the MTHFR gene C677 polymorphisms, functional status (P=0.107), or BDI scores (P=0.848) in study group.

Conclusion: Our study found that the presence of the MTHFR C677T variant was protective against FMS. Based on these results, comprehensive studies in rare types of polymorphisms of MTHFR should be conducted.

Keywords: Fibromyalgia Syndrome, Methylenetetrahydrofolate reductase gene, C677T mutation, Depression

Öz

Amaç: Fibromiyalji sendromu (FMS); etiyolojisi belli olmayan, yaygın vücut ağrıları ve hassas noktalar ile karakterize bir hastalıktır. Oluşumunda pek çok mekanizma öne sürülmüş olup bunlardan biri de kalıtsal mekanizmadır. Hastalığa, en sık depresyon olmak üzere çeşitli ruhsal bozuklukların eşlik ettiği bilinmektedir. Metilentetrahidrofolat redüktaz (MTHFR) gen polimorfizmiyle de depresyon, anksiyete, bipolar bozukluk ve şizofreni gibi psikiyatrik hastalıklar ilişkili bulunmuştur. Bu bilgilerden yola çıkarak FMS tanılı hastalarda etyolojik açıdan MTHFR geni C677T genotipi ve allel sıklığını ve bu genotip ile fibromiyalji kliniği arasındaki olası ilişkiyi belirlemeyi amaçladık.

Yöntemler: Vaka-kontrol çalışmamıza 1990 American College of Rheumatology sınıflama kirterlerine göre tanı konmuş 100 FMS tanılı hasta dahil edildi. Kontrol grubuna ise aynı cinsiyet ve yaş aralığında 100 sağlıklı gönüllü dahil edildi. Katılımcılardan elde edilen periferal kan lökositlerinden genomik DNA ekstrakte edildi ve gerçek zamanlı polimeraz zincir reaksiyonu kullanılarak MTHFR C677T mutasyon tespiti yapıldı. FMS hastalık fonksiyonel durumu Fibromiyalji Etki Anketi (FEA) ve depresyon varlığı Beck Depresyon Envanteri (BDE) ile belirlendi.

Bulgular: Çalışmaya alınan 100 FMS tanılı hasta ve 100 kontrol grubunun hepsi kadındı. Çalışmamızda FMS'lu 100 hastanın 42'sinde (%42) depresyon saptandı. Yapılan istatistiki değerlendirmeler sonucu C allelini taşıyanların T allelini taşıyanlara göre hastalığa yakalanma olasılığı 2,111 kat daha fazla olarak hesaplandı (P<0,001). Hasta grubunda MTHFR geni C677T genotipi polimorfizmi dağılımı ile FEA ve BDE skorları arasında herhangi bir ilişki bulunamadı.

Sonuç: Çalışmamıza göre MTHFR C677T varyantının varlığının FMS'ye karşı koruyucu olduğunu bulundu. Bu sonuçlara dayanarak, MTHFR'nin nadir görülen polimorfizm tiplerinde kapsamlı çalışmalar yapılmalıdır.

Anahtar kelimeler: Fibromiyalji sendromu, Metilentetrahidrofolat redüktaz geni, C677T mutasyonu, Depresyon

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Introduction

Fibromyalgia syndrome (FMS) is characterized by presence of chronic widespread pain, persisting for more than 3 months, without any obvious organic lesion. FMS is often accompanied by additional symptoms such as fatigue, uncomfortable sleep, joint stiffness, cognitive dysfunction, psychological distress, abdominal disturbance, and headache [1-3]. This list also includes depressive symptoms, with a life-time prevalence of 90% for depression and 62-86% for major depressive disorder [4]. The high incidence of depression in FMS suggests that there may be a common pathophysiological mechanism [5]. The etiopathogenesis of FMS is complex and still not fully understood. The strong familial aggregation reported in FMS, though not excluding a possible contribution by environmental factors, appears to point to molecular basis as an important contributor to its etiology [6].

One of the best strategies for evaluating genetic relationships is the analysis of a relatively large number of candidate genes. One of the candidate genes for the development of FMS is methylenetetrahydrofolate reductase (MTHFR), which is a regulatory enzyme of homocysteine (Hcy) metabolism. The MTHFR gene is located on the short arm of chromosome 1 at 1p36.22. The enzyme plays a central role in folate metabolism by irreversibly converting 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, the predominant circulating form of folate. 5-Methylenetetrahydrofolate donates a methyl group to Hcy in the generation of S-adenosyl methionine, a major source of methyl groups in the brain [7]. A common mutation of MTHFR C677T has been shown to cause increased plasma Hcy levels which in turn is associated with an increased risk of vascular disease and hypercoagulability [8]. Particular emphasis has been placed on two common mutations in MTHFR genes: C677T and A1298C. These mutations have been associated with diseases such as cerebrovascular disease, venous thrombosis, neural tube defects, diabetes, cancer, migraine, depression, cognitive impairment, bipolar disorder, and schizophrenia [9,10]. It has been suggested that the mutations in MTHFR gene may be associated with chronic widespread pain [11]. Since FMS is associated with depression, we aimed to investigate the association of FMS and MTHFR genotype.

Whether FMS and some neuropsychiatric disorders share the same etiopathogenesis and they are separate entities that coincidentally have the same alterations in gene locus are unknown. The purpose of this study was to establish the relationship between FMS and C677T genotype of MTHFR gene.

Materials and methods

Patient selection

One-hundred patients with FMS admitted to the Department of Physical Medicine and Rehabilitation at Başkent University Medical Faculty Ankara Hospital between 2013 July and 2014 January were included in the study. The American College of Rheumatology (ACR) 1990 classification for FMS was used in the diagnosis (widespread pain over three months, and tenderness in at least 11 of 18 tender point sites) of FMS. Control group consisted of 100 healthy volunteers, randomly selected among people who visited general health clinics and had no FMS or chronic pain. The FMS and the control groups were all female. All patients provided written informed consent after being informed of the details of the study.

Exclusion criteria included: being under 18 years of age, pregnancy, and chronic diseases such as chronic kidney disease, hypothyroidism, polyneuropathy, and rheumatoid arthritis. All participants were of Turkish descent and shared common ethnogeographic origin.

Clinical evaluation protocol

All participants underwent a complete clinical evaluation. All patients completed a detailed form on demographic characteristics, body mass index and systemic diseases. In addition, peripheral venous blood samples were obtained from all participants for genotyping.

The functional status of the patients included in the study group was assessed using the Fibromyalgia Impact Questionnaire (FIQ) [12], which measures physical function, work status (days of work and work difficulties), depression, anxiety, morning fatigue, pain, stiffness, fatigue and well-being. The FIQ is completed by the patients themselves and the maximum score is 100. In this questionnaire, while a patient with fibromyalgia averages 50 points, a highly affected patient usually obtains more than 70 points. It has been found valid and reliable in Turkish fibromyalgia patients [13].

The participants were also evaluated for depression and health-related quality of life. Depressive symptoms were assessed using the Beck Depression Inventory (BDI), whose validity and reliability in Turkish patients has been proven [14]. A 36-item Short Form Health Survey (SF-36) was used to assess the health-related quality of life of patients and their general health status. The SF-36 is a generic health survey that measures the physical and mental health status of patients. Responses to each of the SF-36 items are scored and summed according to a standardized scoring protocol and expressed as a score on a 0-100 scale for each of the eight health concepts. The higher the score, the better the person perceives his or her health. The SF-36 questionnaire was shown valid and reliable in Turkish patients [15].

Molecular analysis

All patients included in this study gave their informed consent to having a blood sample drawn for DNA analysis. Genomic DNA was extracted from peripheral blood leukocytes by means of a highly pure polymerase chain reaction (PCR) template preparation kit (Roche Diagnostics GmbH, Mannheim, Germany). MTHFR C677T mutation detection was performed by real-time polymerase chain reaction (RT-PCR) using the LightCix Kit and Light Cycler Fast Start DNA Master HybProbe in Light Cycler 2.0 (Roche Diagnostics, Germany). A 233 bp fragment of the MTHFR gene was amplified with specific primers. The resulting PCR fragments were analyzed with hybridization probes and the genotype was identified by melting curve analysis. Melting temperatures were 63.0 °C for 677 C and 54.5. °C for 677 T. CC (Alanin/Alanin) homozygous normal, CT (Alanin/Valin) heterozygote and TT (Valin/Valin) homozygote mutant genotypes are observed in the C677 genotype of MTHFR.

This study was approved by Baskent University Medical and Health Sciences Research Board and Ethics Committee on 09/01/2013 (Project no: KA12 / 274) and supported by Baskent University Research Fund. All subjects understood the purpose of this study and provided their written informed consent prior to their participation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The data set was evaluated using the SPSS program (SPSS version 17.0; SPSS Inc., Chicago, IL, USA). The normal distribution of continuous variables was controlled using the Shapiro-Wilk test. The homogeneity of the variances was analyzed using the Levene test. It has been observed that there are no preconditions for parametric tests. Therefore, the Mann-Whitney U test was used to compare two groups of the subject variables. The results were expressed as mean (standard deviation) and median values. Bi-directional tables were assessed using the Monte Carlo simulated Pearson Chi-square test and Fisher's Exact test. Results were expressed in n and %. *P*-value less than 0.05 was regarded statistically significant.

Results

The demographic characteristics of the patients and controls are given in Table 1. The patients and the controls included in the study were all female, with mean ages of 39.16 (11.62) years in study group and 36.76 (8.74) years in the control group. Symptoms were significantly more (P=0.04) in the study group than in the control group except for Raynaud's phenomenon (P=0.735) (Table 2). According to the FIQ score, 78% of the patients were mildly affected and 22% of the patients were severely affected by FMS. Depression was detected in 42% of FMS patients. There was a statistically significant difference between study and control group in SF-36 health survey scores (P<0.001) (Table 3). The distribution of the C677T genotype of the MTHFR gene in the study and control groups is shown in Table 4. It was found that those who carry the 677 C allele are 2.111 times more likely to have FMS than those carrying the 677 T allele of the MTHFR gene (P<0.001). There was no relationship between distribution in the MTHFR gene C677 polymorphisms and functional status (P=0.107) in study group (Table 5). Similarly, there was no relationship between distribution in the MTHFR gene C677 polymorphisms and BDI scores (P=0.848) in study group (Table 6).

Table 1: The demographic features of FMS patients and controls

	Study group (n = 100)	Control group (n = 100)	*P*-value
Age (years) [mean (SD)]	39.16 (11.62)	36.76 (8.74)	0.289
Body mass index (kg/m²) [mean (SD)]	25.17 (3.82)	25.11 (4.47)	0.715
Education [n (%)]			0.587
Illiterate	1 (1%)	0	
Primary School	25 (25%)	18 (18%)	
Secondary School	7 (7%)	8 (8%)	
High School	28 (28%)	27 (27%)	
University	39 (39%)	47 (47%)	
Marital status [n (%)]			0.860
Single	18 (18%)	21 (21%)	
Married	77 (77%)	74 (74%)	
Widow	3 (3%)	4 (4%)	
Divorced	2 (2%)	1 (1%)	

FMS: Fibromyalgia syndrome, SD: Standard deviation

Table 2: The clinical characteristics of FMS patients and controls

	Study group (n = 100)	Control group (n = 100)	*P*-value
Morning stiffness	77 (77)	5 (5)	0.002
Sleep disorder	79 (79)	15 (15)	0.003
Fatigue	100 (100)	45 (45)	0.004
Morning fatigue	93 (93)	22 (22)	0.003
Irritable bowel syndrome	55 (55)	20 (20)	0.004
Sicca symptoms	21 (21)	5 (5)	0.003
Swelling sensation	67 (67)	7 (7)	0.003
TMJ dysfunction	21 (21)	6 (6)	0.003
Reynaud's phenomena	2 (2)	1 (1)	0.735

FMS: fibromyalgia syndrome, TMJ: temporomandibular joint

Table 3: Comparison of SF-36 health survey outcomes in FMS patients and controls

SF-36	Study group [mean (SD)]	Control group [mean (SD)]	*P*-value
Physical function	60.48 (20.44)	81.66 (15.19)	<0.001
	60.00 (5.00-100.00)	84.00 (50.00-100.00)	
Role physical	74.50 (30.97)	44.50 (47.97)	<0.001
	25.00 (0-100.00)	100.00 (0-100.00)	
Bodily pain	65.69 (21.28)	37.47 (17.00)	<0.001
	41.00 (0-88.00)	63.00 (22.00-100.00)	
General health	44.28 (14.97)	62.85 (15.65)	<0.001
	45.00 (0-80.00)	65.00 (25.00-100.00)	
Vitality	32.6 5 (18.56)	50.73 (18.49)	<0.001
	30.00 (0-75.00)	50.00 (5.00-90.00)	
Social functioning	49.42 (18.94)	68.77 (20.96)	<0.001
	50.00 (0-100.00)	68.75 (12.5-100.00)	
Role emotional	43.65 (29.10)	62.49 (30.10)	<0.001
	33.30 (0-100.00)	66.70 (0-100.00)	
Mental health	50.52 (16.44)	62.36 (17.67)	<0.001
	52.00 (8.00-80.00)	68.00 (20.00-100.00)	

FMS: fibromyalgia syndrome, SF-36: 36-item short form health survey

Table 4: Distribution of the C677 genotypes in study and control groups

	MTHFR (C677) Genotype			
	CC n (%)	TT n (%)	CT n (%)	*P*-value
Study group	58 (58)	6 (6)	36 (36)	<0.001
Control group	37 (37)	17 (17)	46 (46)	

FMS: fibromyalgia syndrome, MTHFR: methylenetetrahydrofolate reductase

Table 5: The relationship between distribution in the MTHFR gene C677 polymorphisms and FIQ scores in study group

	MTHFR (C677) Genotype			
	CC n (%)	TT n (%)	CT n (%)	*P*-value
FIQ<70 (Mild clinical involvement)	39 (39)	3 (3)	30 (30)	0.107
FIQ>70 (Severe clinical involvement)	19 (19)	3 (3)	6 (6)	

FMS: fibromyalgia syndrome, MTHFR: methylenetetrahydrofolate reductase, FIQ: fibromyalgia impact questionnaire

Table 6: The relationship between distribution in the MTHFR gene C677 polymorphisms and depression in study group

	MTHFR (C677) Genotype			
	CC n (%)	TT n (%)	CT n (%)	*P*-value
No depression	33 (33)	3 (3)	22 (22)	0.848
Depression	25 (25)	3 (3)	14 (14)	

FMS: fibromyalgia syndrome, MTHFR: methylenetetrahydrofolate reductase

Discussion

This study aimed to investigate the genetic basis of FMS etiopathogenesis. Therefore, all participants included in the study were female so to exclude the possible differences in genetic and clinical parameters that gender causes. There were no significant differences in the demographical characteristics between FMS patients and controls.

The findings obtained from previous studies show that both genetic factors and abnormal peripheral and/or central pain mechanisms play a role on the development of widespread and chronic pain in FMS patients. According to recent genetic studies, the fact that pain severity is unique to each individual, even though the disease or damage are the same, is explained by genetic polymorphisms [16]. Recent studies have shown that the number of polymorphisms in the serotonin 5-HT2A receptor, dopamine D4 receptor, catechol-O-methyltransferase, adrenergic receptor, IL-4, guanosine triphosphate cyclohydrolase-1 and alpha-1 antitrypsin genes were high in patients with FMS. On the

other hand, these gene variants are not specific to FMS and can also be observed in other somatic disorders [17,18].

It has been suggested that in those who are genetically predisposed to FMS, psychological factors trigger the development of fibromyalgia [19]. It has also been reported that FMS is more common in families with mood disorders and it is suggested that these two conditions may result from a common genetic predisposition [20]. According to some investigators, irritable colon, panic disorders and major affective disorder are different clinical manifestations that originate from the same pathology [2,21,22].

In various studies, the incidence of psychiatric comorbidity in FMS has been reported between 30% and 60% [4,23,24]. In these patients, specific disorders such as depression and anxiety, somatization, panic disorder are seen [4]. In the studies in our country, Guven et al. [25] evaluated the depressive symptoms of FMS patients using BDI and detected mild (50%), moderate (38%) and severe (2%) depression in the patients. In our study, depression was found in 42% of FMS patients, consistent with these results.

There is compelling evidence that mood disorders including depression are significantly affected by polygenic and multifactorial genetic factors. MTHFR enzyme catalyzes the transformation of methylenetetrahydrofolate into tetrahydrofolate. The point where this reaction takes place is a junction which affects DNA methylation, folic acid, homocysteine, and nucleotide synthesis. Several mutations have been reported in the MTHFR gene. The most common, MTHFR C677T, is the transition of cytosine to thymine in 4th exon, 677th position. In patients with MTHFR mutations, reduced enzyme activity and decreased remethylation of hcy to methionine leads to elevated total Hcy. As Hcy promote oxidant injury to vascular cells, hyperhomocysteinemia may play an important role in oxidative stress [26].

Clinical characteristics such as peripheral neuropathy, developmental deficiency, hypotonia, stroke and thrombosis are observed in serious MTHFR deficiency in which hyperhomocysteinaemia and homocysistinuria occur. Mild and moderate MTHFR deficiency is common, reported in 10-15% of the general population. Such patients suffer from various diseases such as neurological diseases like dementia, Alzheimer, Parkinson's disease and migraine, chronic fatigue syndrome, and psychiatric disorders such as depression, anxiety, schizophrenia, and bipolar disorder. Furthermore, Schmechel and Edwards stated that MTHFR mutation may be associated with chronic widespread pain and FMS [11].

Arinami et al. [27] found that there was a significant relationship between the MTHFR C677T, in particular the homozygous TT (T allele) variant, and patients with depression and schizophrenia. Almeida et al. [28] investigated the relationship between MTHFR C677T genotype and depression, anxiety and cognitive disorders and observed that TT genotype patients were inclined to becoming depressed. However, there was no correlation between MTHFR genotype, anxiety and cognitive impairment. Similarly, in this article, the relationship between MTHFR C677T and depression is explained by mechanisms involving impaired cellular methylation, critical for the synthesis and metabolism of norepinephrine, serotonin, and dopamine. In our study, we did not find any relationship between polymorphism and patients diagnosed with depression (P=0.848) in the study group (Table 6).

A meta-analysis by Gilbody et al. [29] showed that subjects with the TT genotype of MTHFR had an increased risk of depression. On the other hand, there was no correlation between MTHFR C677T and anxiety disorders in this meta-analysis. In another meta-analysis, the relationship between MTHFR gene variants and psychiatric disorders such as schizophrenia, bipolar disorder and unipolar depressive disorder was investigated, and TT genotype carriers were found to be more at risk than CC genotype carriers [9].

The first study published in the literature investigating the relationship between FMS and MTHFR C677T was performed by Inanir et al. [26]. This study, conducted among Turkish patients, showed that there was no significant correlation between MTHFR C677T mutation and FMS, but that MTHFR C677T mutation was significantly associated with findings of dry eye and feelings of stiffness. The authors emphasized that the MTHFR C677T mutation was also reported in patients with Sjögren's syndrome and eye involvement in Behçet's disease. They stated that this mutation may be involved in the complex mechanism of dry eye, which in turn may be related to FMS.

In our study, we found that the likelihood of developing FMS in 677 C alleles was 2.111-fold higher than that of the 677 T allele carriers of the MTHFR gene. That is, CC genotype carriers (normal genotype) were more prone to FMS when compared to TT genotype carriers (homozygous mutant) of the MTHFR gene. Also, when the distribution in C677T genotype of MTHFR was compared to FIQ points, no relationship was found between genotype distribution and severity of fibromyalgia. Although there is a relationship between MTHFR C677T homozygosity and depression in the literature, there is no study showing that it is associated with anxiety disorders [28,29]. However, as in our study, we did not observe a study showing protection in TT genotype carriers. Our results may be explained by the fact that normal genotype pattern (CC) is more common in the population.

Limitation

In this study, C677T, the most frequent genotype of the MTHFR gene, was investigated, however the second frequent polymorphism of the MTHFR gene, 1298C, was not. This may be considered a limitation of the study. Another limitation of the study is that the number of participants was relatively small.

Conclusion

Our study was based mainly on the fact that MTHFR C677T gene polymorphism is considered an etiological factor in the development of depression and the frequent coexistence of psychiatric diseases in fibromyalgia syndrome patients. However, while MTHFR C677 TT carriage is thought to predispose to depression and other psychiatric diseases, it was found to be protective against FMS in our study. Based on these results, future comprehensive studies on rare types of polymorphisms of MTHFR should be conducted.

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